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Workshop
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Le opportunità di un linguaggio comune 3ª ed.

Como, 1-2 aprile 2006

SNAMID
Sezione di Como

Workshop Clinici Interattivi (4)

La valutazione del rischio tromboembolico tra credenze ed evidenze: quale ruolo per il MMG?

Maurizio Mancuso
Angelo Beretta

Scenario Clinico

• Ilaria è una giovane donna di 30 anni che conosco da quando era bambina.

• E' figlia unica e non ha nessuna patologia di rilievo nella storia personale

• E' una donna molto forte ed appena maggiorenne ha incominciato a girare il mondo grazie al suo lavoro molto dinamico (fotografa freelance per diverse riviste)

• E' leggermente sovrappeso (BMI 27), fuma 10 sigarette al dì e assume da oltre 5 anni una pillola di terza generazione, non pratica attività fisica (se non sporadicamente)

Scenario Clinico

• Vedo Ilaria al ritorno dal Sud America.

• Riferisce una storia di diarrea acquosa (4-6/scariche da circa 7 giorni), associata ad inappetenza e febbre (max 38.5 °C solo il primo giorno).

• Ha utilizzato un sintomatico (di cui non ricorda il nome) senza alcun beneficio.

• Inoltre, lamenta fastidiosi crampi al polpaccio destro

Scenario Clinico

• L'obiettività clinica è negativa: nulla di rilevante a livello addominale, la cute e le mucose sono rosee, non evidenti segni di disidratazione, il polpaccio dx è morbido, senza edemi né dolorabilità.

• Richieso 3 ricerche dei parassiti nelle feci ed una coprocoltura.

• Prescrivo soluzione salina (potassio e magnesio) 2 bustine/die e ciprofloxacina 500 mg (2 crp/die per 3 giorni) da iniziare dopo la coprocoltura.

Scenario Clinico

• Dopo quattro giorni, Ilaria torna in studio: non ha eseguito gli accertamenti, nè ha assunto l'antibiotico perché la diarrea si era risolta spontaneamente.

• Tuttavia, persiste il fastidio al polpaccio, costantemente dolente.

• Obiettivamente:
  - non si riscontrano edemi né differenza di circonferenza fra dx e sin.
  - non dolorabilità sia alla compressione, sia evocando il segno di Homans.

Scenario Clinico

• Unica alterazione è la minima percezione di alcune formazioni vermiformi al poplite con lievissima pastosità dei tessuti circostanti.

• Nel sospetto di una trombosi venosa profonda richiedo un eco-colordoppler urgente e somministro enoxaparina (6.000 UI).

CLINICAL QUESTIONS

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A. Quanto stimi la probabilità (pre-test) di trombosi venosa profonda in una paziente come Ilaria

1. Bassa
2. Intermedia
3. Elevata

Scottish Intercollegiate Guidelines Network

62 Prophylaxis of Venous Thromboembolism

A national clinical guideline

Scottish Intercollegiate Guidelines Network

Age	Exponential increase in risk with age. In the general population - <40 years annual risk 1/10,000 60-69 years annual risk 1/1,000 >80 years annual risk 1/100 May reflect immobility and coagulation activation
Obesity	1 x risk if obese (body mass index >30 kg/m²) May reflect immobility and coagulation activation
Varicose veins	1.5 x risk after major general / orthopaedic surgery But low risk after varicose vein surgery
Previous VTE	Recurrence rate 5% / year, increased by surgery
Thrombophilias	Low coagulation inhibitors (antithrombin, protein C or S) Activated protein C resistance (e.g. factor V Leiden) High coagulation factors (I, II, VIII, IX, XI) Antiphospholipid syndrome High homocysteine
Other thrombotic states	Malignancy 7 x risk Heart failure Recent myocardial infarction / stroke Severe infection Inflammatory bowel disease, nephrotic syndrome Polycythaemia, paraproteinaemia Bechet's disease, paroxysmal nocturnal haemoglobinuria
Hormone therapy	Oral combined contraceptives, HRT, raloxifene, tamoxifen 3 x risk High dose progestogens 6 x risk (see section 10)
Pregnancy, puerperium	10 x risk (see section 9)
Immobility	Bedrest >3 days, plaster cast (see section 5), paralysis (see sections 5 &7) 10 x risk, increases with duration
Prolonged travel	see section 11
Hospitalisation	Acute trauma, acute illness, surgery, 10 x risk
Anaesthesia	2x general vs spinal / epidural

Goodacre S, Sutton A J, Sampson FC

Meta-analysis: the value of clinical assessment in the diagnosis of deep venous thrombosis

Ann Intern Med 2005;143:129-139

Context

Which clinical findings most affect the probability of deep venous thrombosis (DVT)?

Contribution

This systematic review of 54 cohort studies found that previous DVT and malignant disease modestly increased the probability of DVT (positive likelihood ratios, 2.25 and 2.71), followed by recent immobilization, difference in calf diameter, and recent surgery (positive likelihood ratios, 1.75 to 1.98). Wells scores, based on 9 items, stratified patients' probability of proximal DVT much better than did individual findings, particularly in younger patients and in patients without previous DVT.

Implications

Estimating the probability of DVT is best accomplished by assessing and scoring multiple findings.

Goodacre S, et al . Ann Intern Med, 2005

Pooled likelihood ratios of individual clinical features, the Wells risk score, and physicians' empirical assessment for detecting the presence or absence of deep venous thrombosis (DVT)*

Diagnostic test	Number of studies	+LR (95% CI)	−LR (CI)
Malignant disease	20	2.7 (2.2 to 3.4)	0.89 (0.85 to 0.93)
History of DVT	11	2.3 (1.6 to 3.2)	0.90 (0.85 to 0.95)
Recent immobilization	17	2.0 (1.7 to 2.3)	0.90 (0.85 to 0.94)
Recent surgery	17	1.8 (1.4 to 2.2)	0.94 (0.91 to 0.97)
Difference in calf diameter	8	1.8 (1.5 to 2.2)	0.57 (0.44 to 0.72)
Calf swelling	16	1.5 (1.3 to 1.7)	0.67 (0.58 to 0.78)
Wells risk score	22		
High risk		5.2 (4.0 to 6.0)	—
Low risk		—	0.25 (0.21 to 0.29)
Empirical assessment	4		
High risk		5.6 (1.9 to 16.6)	—
Low risk		—	0.20 (0.10 to 0.41)

Table 1. **The Wells Rule To Estimate the Probability of Deep Venous Thrombosis**

Clinical Feature	Score
Active cancer	1
Paralysis, paresis, or recent plaster immobilization of the lower extremity	1
Recently bedridden for more than 3 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or more possible than that of deep venous thrombosis	−2

Low risk score ≤ 0
Medium risk score 1-2
High risk score ≥ 3

Fancher TL, White RH, Kravitz RL.

Combined use of rapid D-dimer testing and estimation of clinical probability in the diagnosis of deep vein thrombosis: systematic review

BMJ 2004;329:821-4

Table 3 Thromboembolic outcomes using SimpliRED or the highly sensitive D-dimer test

Potential testing scheme	Three month cumulative incidence of venous thromboembolism in % (95% CI)
Normal SimpliRED D-dimer result plus:	
Low clinical probability	0.5 (0.07 to 1.1)
Moderate clinical probability	3.5 (1.4 to 6.9)
High clinical probability	21.4 (8.5 to 37.9)
Normal highly sensitive D-dimer result plus:	
Low or moderate clinical probability	0.4 (0.04 to 1.1)
High clinical probability	6.4 (1.7 to 14.5)

Fancher TL, et al . BMJ 2004

Oudega R, Hoes AW, Moons KGM

The Wells rule does not adequately rule out deep venous thrombosis in primary care patients

Ann Intern Med 2005;143:100-107

Context

Physicians sometimes use a 9-item clinical rule (the Wells rule) to assess probability of deep venous thrombosis (DVT). In the original study that developed the Wells rule, only 3% of patients who were classified as low risk by the rule had DVT.

Contribution

A total of 110 primary care physicians assessed 1295 consecutive outpatients with symptoms suggestive of DVT and then referred them to hospitals for diagnosis with leg ultrasonography. Twelve percent of patients who were classified as low risk by the physicians' Wells rule assessments had DVT.

Implications

Low-risk categorization by the Wells rule may not safely rule out DVT in all primary care patients.

Oudega R, et al . Ann Interm Med, 2005

Operating characteristics of the Wells rule, with and without the D-dimer test, for identifying primary care patients with deep venous thrombosis*

Definition of a negative test	Sensitivity (95% CI)	Specificity (CI)	Negative predictive value (CI)	−LR (CI)
Wells score ≤ 0	79% (74 to 84)	44% (41 to 47)	88% (85 to 91)	0.48 (0.38 to 0.60)
Wells score ≤ 0 and normal D-dimer test	98% (97 to 100)	22% (19 to 24)	98% (96 to 100)	0.08 (0.03 to 0.19)

Oudega R, et al . Ann Interm Med, 2005

Douketis JD

Use of a clinical prediction score in patients with suspected deep venous thrombosis. Two steps forward, one step back?

Ann Intern Med 2005;143:140-142

CLINICAL QUESTIONS

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B. Condividi la decisione del collega di iniziare il trattamento con LMWH prima di una conferma diagnostica della TVP?

1. No
2. Sì

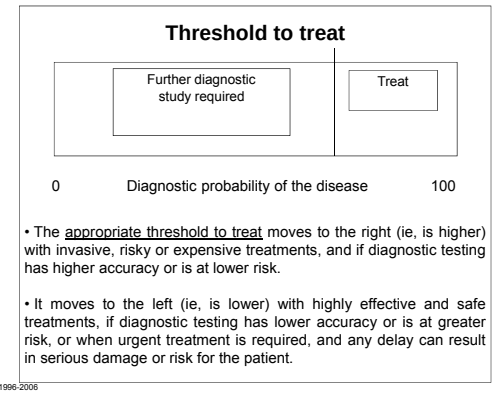
7th American College of Chest Physicians (ACCP) Conference on Antithrombotic and ThrombolyticTherapy

Antithrombotic Therapy for Venous Thromboembolic Disease

Chest 2004;126:401S-428S

1.1.2. For patients with a high clinical suspicion of DVT, we recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (**Grade 1C+**).

ACCP, 2004



• The appropriate threshold to treat moves to the right (ie, is higher) with invasive, risky or expensive treatments, and if diagnostic testing has higher accuracy or is at lower risk.

• It moves to the left (ie, is lower) with highly effective and safe treatments, if diagnostic testing has lower accuracy or is at greater risk, or when urgent treatment is required, and any delay can result in serious damage or risk for the patient.

Scenario Clinico

• L'eco-colordoppler evidenzia: "TVP parcellare gemellare mediale al terzo prossimale del polpaccio dx. Flusso modulato dal respiro in femorale comune".

• Viene proposto ricovero ospedaliero, che la paziente rifiuta.

CLINICAL QUESTIONS

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C. Ritieni appropriato il ricovero ospedaliero per il trattamento della TVP?

1. Sì
2. No

Schraibman IG, Milne AA, Royle EM

Home versus in-patient treatment for deep vein thrombosis

The Cochrane Database of Systematic Reviews 2006, Issue 1

MAIN RESULTS

• Three RCTs (1101 patients) with several problems: high exclusion rates, partial hospital treatment of many in the LMWH arms, and comparison of UHF in hospital with LMWH at home.

• Home treatment was no more liable to complications than hospital treatment: recurrence of venous thromboembolism, minor bleeding, major bleeding, and crude death rate were not statistically significant.

Schraibman IG, et al. Cochrane Library 2006

AUTHORS' CONCLUSIONS

• The limited evidence suggests that home management is cost effective, and likely to be preferred by patients.

• Further large trials comparing these treatments are unlikely to be held.

• Therefore, home treatment is likely to become the norm, and further research will be directed to resolving practical issues.

Schraibman IG, et al. Cochrane Library 2006

Scenario Clinico

• Viene confermata la terapia con enoxaparina (6.000 UI x 2 x 5 giorni) a cui viene imbricata, dopo alcuni giorni, terapia con warfarin (INR tra 2-3), da continuare per 3 mesi.

CLINICAL QUESTIONS

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D. Ritieni appropriato il trattamento prescritto per il trattamento della TVP?

1. Sì
2. No, avrei prescritto solo l'enoxaparina
3. No, avrei prescritto solo l'anticoagulante orale

Recommendations

1.1.1. For patients with objectively confirmed DVT, we recommend short-term treatment with SC LMWH or IV UFH or SC UFH (**all Grade 1A**).

1.1.2. For patients with a high clinical suspicion of DVT, we recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (**Grade 1C+**).

1.1.3. In acute DVT, we recommend initial treatment with LMWH or UFH for at least 5 days (**Grade 1C**).

1.1.4. We recommend initiation of VKA together with LMWH or UFH on the first treatment day and discontinuation of heparin when the INR is stable and > 2.0 (**Grade 1A**).

ACCP, 2004

CLINICAL QUESTIONS

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E. Nel trattamento della TVP, ritieni appropriata la durata del trattamento con warfarin (3 mesi)?

1. Sì
2. No, la durata è eccessiva
3. No, la durata è insufficiente

Hutten BA, Prins MH

Duration of treatment with vitamin K antagonists in symptomatic venous thromboembolism

The Cochrane Database of Systematic Reviews 2006, Issue 1

MAIN RESULTS

• Eight studies (2.994 patients) were included.

• A consistent reduction in the risk of recurrent events was observed during prolonged treatment with vitamin K antagonists (RRR 72%; 95% CI (74-87%).

• A substantial increase in bleeding complications was found during the entire period after randomization (OR 2.62; 95% CI 1.48 to 4.61).

Hutten BA, et al. Cochrane Library 2006

AUTHORS' CONCLUSIONS

• Treatment with vitamin K antagonists reduces the risk of recurrent venous thromboembolism for as long as it is used.

• However, the absolute risk of recurrent venous thromboembolism declines over time, while the risk for major bleeding remains.

• Thus, the efficacy of vitamin K antagonist administration decreases over time since the index event.

Schraibman IG, et al. Cochrane Library 2006

2.0 Long-term Treatment of Acute DVT of the Leg

2.1 Vitamin K antagonists for the long-term treatment of DVT

2.1.1. For patients with a first episode of DVT secondary to a transient (reversible) risk factor, we recommend long-term treatment with a VKA for 3 months over treatment for shorter periods (**Grade 1A**).

Underlying values and preferences. This recommendation ascribes a relatively high value to preventing recurrent thromboembolic events and a relatively low value on bleeding and cost.

Remark: The latter recommendation applies both to patients with proximal vein thrombosis, and to patients with symptomatic DVT confined to the calf veins.

ACCP, 2004

Scenario Clinico

• Dopo un mese dall'inizio della terapia, su consiglio di un altro specialista esegue un secondo eco-colordoppler, nella speranza di interrompere il trattamento.

• L'indagine rileva ancora materiale trombotico occludente la vena gemellare.

• Ribadisco, pertanto, di continuare la terapia con warfarin, mantenendo l'INR tra 2 e 3.

CLINICAL QUESTIONS

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F. In una paziente come Ilaria, ritieni appropriato lo screening dello status trombofilico?

1. No
2. Sì, con PT, PTT, AT-III
3. Sì, 2 + proteina C e proteina S
4. Sì, 2+3 + altri test*

*APC resistance, anticorpi anticardiolipina, LLAC, mutazione del fattore V di Leiden, mutazione G20210A della protrombina, omocisteina

The Thrombophilias: Well-Defined Risk Factors with Uncertain Therapeutic Implications

Kenneth A. Bauer, MD

Ann Intern Med. 2001;135:367-373.

Table 1. Risks for and Incidence of a First Episode of Venous Thrombosis

Variable (Reference)	Relative Risk	Annual Incidence, %
Normal	1	0.008
Hyperhomocysteinemia (5)	2.5	0.02
Homozygous MTHFR C677T mutation (9)	1	
Prothrombin G20210A mutation (3)	2.8	0.02
Oral contraceptive use (10)	4	0.03
Factor V Leiden heterozygote (7)	7	0.06
Oral contraceptive use and factor V Leiden mutation (10)	35	0.3
Factor V Leiden homozygotes (11)	80	0.5–1

College of American Pathologists Consensus Conference XXXVI, November 9–11, 2001

College of American Pathologists Consensus Conference XXXVI: Diagnostic Issues in Thrombophilia

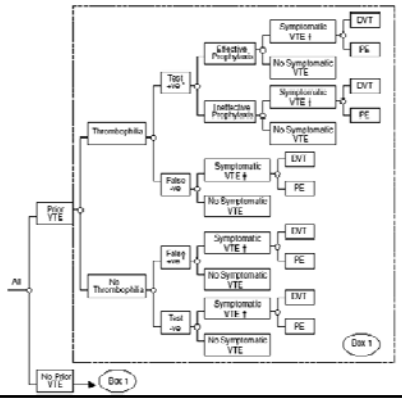
Introduction and General Considerations

RECOMMENDATION

• Testing for thrombophilia is recommended in women who experience VTE as cerebral venous thrombosis during oral contraceptive use or HRT. (Level 1)

bjh research paper

Screening for thrombophilia in high-risk situations: a meta-analysis and cost-effectiveness analysis



• Universal screening of women prior to prescribing hormone replacement therapy was the most cost-effective (ICER £ 6.824).

• Universal screening of women prior to prescribing combined oral contraceptives was the least cost-effective strategy (ICER £ 202.402).

• Selective thrombophilia screening based on previous personal and/or family history of venous thromboembolism was more cost-effective than universal screening in all the patient groups evaluated.

Scenario Clinico

• Dopo venti giorni dal termine della terapia, Ilaria sta bene, non ha più alcun sintomo, ed esegue gli esami di screening per la trombofilia (APC resistance, proteina C, proteina S, antitrombina III, omocisteina, fattore V di Leiden, mutazione G20210A della protrombina, LLAC, ACA) che risultano negativi.

Scenario Clinico

• Ilaria vuole alcuni consigli sullo stile di vita, in particolare sui fattori che possono incrementare il suo rischio tromboembolico (fumo, anticoncezionali), ma soprattutto sulla necessità di una profilassi specifica in occasione dei suoi lunghi e frequenti viaggi aerei.

CLINICAL QUESTIONS

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G. Nei pazienti con pregresso episodio di TVP è indicata profilassi specifica in occasione di lunghi viaggi aerei?

1. No
2. Sì, con calze elastiche a compressione graduata
3. Sì, con aspirina
4. Sì, con EBPM

7th American College of Chest Physicians (ACCP) Conference on Antithrombotic and ThrombolyticTherapy

Prevention of Venous Thromboembolism

Chest 2004;126:338S-400S

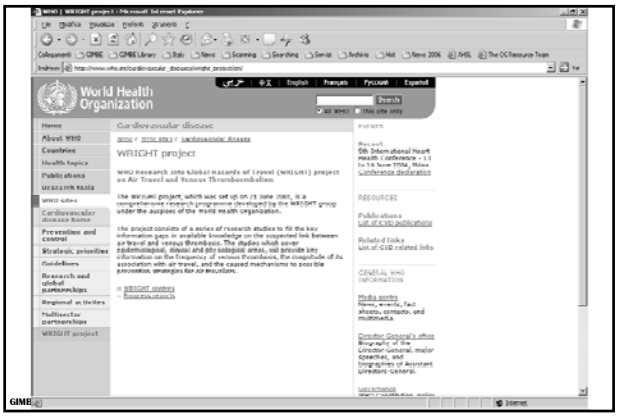
Recommendations: Long Distance Travel

9.1. We recommend the following general measures for long-distance travelers (*ie*, flights of > 6 h duration): avoidance of constrictive clothing around the lower extremities or waist; avoidance of dehydration and frequent calf muscle stretching (**Grade 1C**).

9.2. For long-distance travelers with additional risk factors for VTE, we recommend the general strategies listed above. If active prophylaxis is considered, because of the perceived increased risk of venous thrombosis, we suggest the use of properly fitted, below-knee GCS, providing 15 to 30 mm Hg of pressure at the ankle (**Grade 2B**), or a single prophylactic dose of LMWH, injected prior to departure (**Grade 2B**).

9.3. We recommend **against** the use of aspirin for VTE prevention associated with travel (**Grade 1B**).

ACCP, 2004



Scenario Clinico

• Oggi, dopo 4 anni dall'episodio di TVP, Ilaria ha continuato a viaggiare per il mondo senza alcun disturbo, ad eccezione del timore di una embolia che in alcune occasioni ha generato veri e propri disturbi da attacchi di panico (DAP) che hanno spaventato molto la paziente.

• Ha sospeso la pillola ed è dimagrita di 7 Kg, ma continua a fumare più di prima ("un pacchetto non basta")

• Nel frattempo si è sposata e intende presto avere un figlio

CLINICAL QUESTIONS

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H. Nei pazienti con pregresso episodio di TVP è indicata profilassi specifica in occasione di una gravidanza?

1. No
2. Sì